An association between ICP-derived data and outcome in TBI patients: The role of sample size.

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Abstract

Background: Many demographic and physiological variables have been associated with outcome after TBI. However, with small sample sizes, making spurious inferences is possible. This paper explores the effect of sample sizes on statistical relationships between patient variables (both physiological and demographic) and outcome.

Methods: Data from head-injured patients with monitored arterial blood pressure, intracranial pressure (ICP) and outcome assessed at 6 months were included in this retrospective analysis. A univariate logistic regression analysis was performed to obtain the odds ratio (OR) for unfavourable outcome. Three different dichotomizations between favourable and unfavourable outcomes were considered. A bootstrap method was implemented to estimate the minimum sample sizes needed to obtain reliable association between physiological and demographic variables with outcome.

Results: In a univariate analysis with dichotomized outcome, samples sizes should be generally larger than 100 for reproducible results. Pressure reactivity index, ICP and ICP slow waves offered the strongest relationship with outcome. Relatively small sample sizes may overestimate effect sizes or even produce conflicting results.

Conclusion: Low power tests, generally achieved with small sample sizes, may produce misleading conclusions, especially when they are based only on p-values and the dichotomized criteria of rejecting/not-rejecting the null hypothesis. We recommend reporting confidence intervals and effect sizes in a more complete and contextualized data analysis.

Introduction

Traumatic brain injury (TBI) is a major cause of worldwide morbidity and mortality [1]. Identifying factors that might indicate a poorer prognosis is important for proper management of TBI patients [2]. While, some predictive factors may be related to patient demographics (such as age, sex) and initial factors related to primary injury – as Glasgow coma scale – GCS, other factors may be derived from physiologic variables that can reflect secondary brain injuries and therefore offer the possibility of informing management protocols.

The use of physiological and demographic variables as predictors of patient outcome has been largely discussed in the literature [2–5]. In particular, high time resolution multimodal monitoring allows for an extended assessment of secondary injury after TBI [6]. However, because of difficulties in obtaining large datasets of high resolution physiological signals, some studies have relatively small sample sizes. The failure to find a relationship between a physiological variable (or a derived index) and outcome, where one truly exists (type II statistical error) could prematurely end research on a promising 'physio-marker'. Conversely, finding a spurious relationship between a monitored variable or index when one does not exist (type I statistical error) may take a significant time to be rectified in the scientific community; especially with the acknowledged 'positive results publication bias'.

The objective of this study is to highlight potential pitfalls when only p-values are used to interpret results from relatively small data sets. More specifically, we explored the role of sample size when physiological and demographic variables are associated with patient outcome using univariate binary logistic regression models. In this context, we also estimated the minimum sample sizes needed to obtain reproducible results.

Methods

Data from head-injured patients having full record of monitored variables of interest, connected to a bedside computerized system (solftware: ICM (1992-2003), Warsaw University of Technology , Poland and University of Cambridge , UK and later ICM+® (2003-2015) http://www.neurosurg.cam.ac.uk/icmplus Cambridge Enterprise, Cambridge, UK) with invasive monitoring of ABP and ICP over a period longer than 12 hours were included in this retrospective analysis. ABP was invasively monitored through a catheter in the radial artery; the pressure transducer was zeroed at heart level. ICP was continuously monitored with Codman parenchymal probes (Johnson & Johnson Medical, Raynham, MA, USA) via a cranial access device (Technicam, Abbott, UK). Probes were positioned at a constant depth in the white matter, pericontusional in focal injuries or in the non-dominant frontal lobe in diffuse injuries. Patients were managed according to international TBI guidelines [7]. Patients were sedated, intubated and ventilated. Interventions were aimed at keeping ICP < 20 mm Hg using a stepwise approach of positioning, sedation, neuromuscular paralysis, mild hyperventilation, ventriculostomy, osmotic agents, and induced hypothermia [8]**.** Cerebral perfusion pressure (CPP) was maintained >60 mm Hg using intravenous fluids

and vasopressors. Computerised indices did not form a part of the management algorithm. The Glasgow outcome scale (GOS) was assessed at 6 months by outpatient assessment [9]. The digital recording of high resolution data for further anonymous use in academic publications has been approved by the institutional ethics committee (29 REC 97/291) and local Neurocritical Care Users' Committee.

Patients were divided between two groups, favourable (FAV) and unfavourable (UNF), according to their GOS score: 1 - Death (D); 2 - Persistent Vegetative State (PVS); 3 - Severe disability (SD); 4 - Moderate Disability (MD) and 5 - Good Recovery (GR). The proportions of each GOS score for each variable are presented in Tab.1.

Three different dichotomizations were used in this study: *Dicho1* contains GOS=1 for UNF and GOS 2-5 for FAV. *Dicho 2* comprises GOS 1-2 for UNF and GOS=3-5 for FAV and finally, *Dicho 3* consist of GOS 1-3 and GOS 4-5 for UNF and FAV groups respectively. The demographic variables used for outcome association are: *Age* and Glasgow Coma Scale (*GCS*). The physiological variables were averaged over whole period of NCCU stay. They are: Arterial Blood Pressure (*ABP*); Intracranial Pressure (*ICP*); Amplitude of ICP pulse (*AMP*); magnitude of ICP slow waves (Slow); Cerebral Perfusion Pressure (*CPP*); Pressure Reactivity index (*PRx*); and Compensatory Reserve index (RAP). There is a substantial literature about these indices, for a useful description see [6].

Bootstrapping method

One of the objectives of this study is to obtain the incidence of statistically significant results when different sample sizes are used. The straightforward approach would be to consider all possible combinations of patients from the data set, for a given sample size, and obtain the statistics for each case. However, this would be impracticable since there are approximately 10^{48} possible combinations for a sample size N=30 for example. A more appropriate approach is to use a bootstrapping method to estimate the probability distribution of the chosen statistic.

We examined samples of N=20 up to N=15000. Patients for each N, were randomly chosen with reposition. A univariate logistic regression is applied and the odds ratio (OR) of favourable vs. unfavourable outcome is obtained with its respective p-value. This process was repeated 10000 times for each sample size and for each variable. Thus, we can estimate the minimum sample size required to obtain a statistically significant result in 90% of the drawings.

Results

Using ICP and dichotomization Dicho 1 as an example, Fig.1 presents the box-plots for the odds ratio (OR) as well as the p-values for different sample sizes (N). For small sample sizes the variability of OR and p-values are larger and gets smaller with increasing N. The incidence of significant results increases with sample size, reaching 90% at N=140.

Considering only statistically significant results ($p<0.05$), Fig. 2 compares the OR and 95% confidence interval sizes obtained in 1000 random samples for two different sizes N=30 and N=200. For N=30 (open squares) the values of OR obtained are more dispersed varying from 1.2 to 1.4 and the sizes for the 95% CI are also larger from 0.2 to 0.6. On the other hand, for N=200, the values of OR varies between 1.05 to 1.15 and the 95% CI size is around 0.1. The statistics variability for small sample sizes is responsible for producing conflicting results as pointed out by the arrow in Fig. 2. With the same sample size (N=30), the odds ratio may be statistically significant below one (OR<1) or above one (OR>1).

The minimum sample size (N_{min}) needed to obtain 90% incidence of significant results for each predictor variable considered in this study are presented in Tab. 2. Minimum sample sizes generally decreases for more restrictive conditions for unfavourable outcome, i.e. N_{min} are smaller for Dicho 1 and 2. With the exception of RAP and both demographic variables (Age and GCS) where the addition of SD patients increases the effect sizes and therefore diminishes N_{min}. For CPP and AMP, the inclusion of SD patients in the unfavourable group reduces considerably the associative power of those variables, with estimated N_{min} greater than 15000.

Discussion

In the current analysis, PRx, ICP and ICP slow waves offered the strongest relationship with outcome. This result highlights the importance of impaired pressure reactivity and intracranial hypertension as secondary injuries in TBI [4].

The incidence of p-values below the significance level, obtained through bootstrapping, can be interpreted as an estimate *power* of the test, i.e. its *sensitivity*. It is well described in the literature that power increases with sample size [10]. However, studies with small sample sizes (N=30-50) can be found quite frequently even in good journals and therefore low statistical power are usually employed [11]. Underpowered tests may provide a statistically significant result that not only fails when comes to its reproducibility but also overestimates its clinical relevance; both sensitivity and *positive predictive value* (PPV) are low for underpowered tests [11].

For instance, in a study with N=30 patients the odds ratio that increasing ICP will increase the odds for unfavourable outcome will most likely not be statistically significant, hence one will not have enough evidence that increased ICP is related to worse outcome. Note that this does not imply that increased ICP is not related to worse outcome; the absence of evidence is not the evidence of absence. A non-significant result just means that there is insufficient information to prove the proposition to be either true or false; more data is needed to gather more evidence against the null-hypothesis. But we must keep in mind that a large enough sample will eventually produce a statistically significant result [11] and consequently it should be interpreted in the light of its clinical relevance. Also, a statistically significant result in this scenario will most likely overestimate its effect size and consequently its clinical relevance, the well-known "winner's curse" [12]. Also, the variability of OR and p-values for

small sample sizes may produce misleading conclusions. The conflicting result presented in Fig.2, with significant result for OR>1 and OR<1 illustrates the point that without any additional information other than the dichotomized criteria of rejecting/not-rejecting the null hypothesis, it is difficult to come up with any meaningful conclusions and there are no means to access the reproducibility of the results.

Limitations

The current study considered the use of a univariate logistic regression analysis for outcome association and sample size (N) considered in the analysis is evenly distributed between groups. Although outcome prediction in TBI is obviously a multivariate problem, for the current analysis we wished simply to highlight the importance of considering a more complete description of the statistical results rather than just p-values.

The particular 'optimal sample sizes' (N_{min}) obtained are for illustrative purposes only, rather than a research framework, because it was constructed using data from only one research centre and therefore may not be applicable for other data sets. Furthermore it deals with a specific characteristic of the analysis which is 90% power. There are other alternative criteria to select optimal sample sizes, for instance the "planning for precision", which calculates the sample size required for estimating the effect size to reach a defined degree of precision [13].

Rather than just prescribing a minimum sample size needed for publication of results, the current study highlights potential pitfalls when searching for physiologic indices that predict outcome [14-18]. At least in the field of TBI research, relationships between monitored variables and outcome must be carefully interpreted when sample sizes less than 100 are used. This result only reinforces the importance of multi-center studies when it comes to clinical neuroscience.

Conclusion

Consistent with other opinion, we recommend a more complete and contextualized description of results . Sample size, effect size, power and confidence intervals should all be considered in addition to p-values when interpreting results from statistical inferences. Relying only in p-values as the final word can produce misleading conclusions, especially when combined with the dichotomized criteria of rejecting/not-rejecting the null hypothesis.

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Conflict of interest: ICM+ is a software licensed by Cambridge Enterprise Ltd, UK. PS and MC have financial interest in a fraction of the licensing fee. The remaining authors declare no conflicting interests.

Figure Captions

Figure 1: Considering ICP as the predictor variable, in **(a)** box-plot of the Odds Ratio and respective p-values in **(b)** as a function of sample size N obtained in 10^5 tests. In **(c)** the incidence of p-values below the significance level of 5%. The larger the sample size, the better is the reproducibility of the result. Arrows indicate the minimum sample size for ICP (N_{min} = 100) in order to obtain reproducible results 90% of the time.

Figure 2: Considering only significant results ($p<0.05$), odds ratio and 95% confidence interval sizes for 1000 results with sample size N=30 and N=200. For small sample sizes (open squares) the obtained effect size (OR) is overestimated, the so called "winner's curse" and the confidence intervals are larger. Also, the arrow points to possible conflicting results (OR<1) that may occur when sample sizes are small.

Table 1: Number of patients for each variable and the proportions among different GOS scores.

Table 2: Estimated minimum sample sizes (N_{min}) required for each physiological variable for 90% incidence of p-values below 0.05. Tests were performed considering different dichotomizations between favourable and unfavourable outcomes.

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Figure

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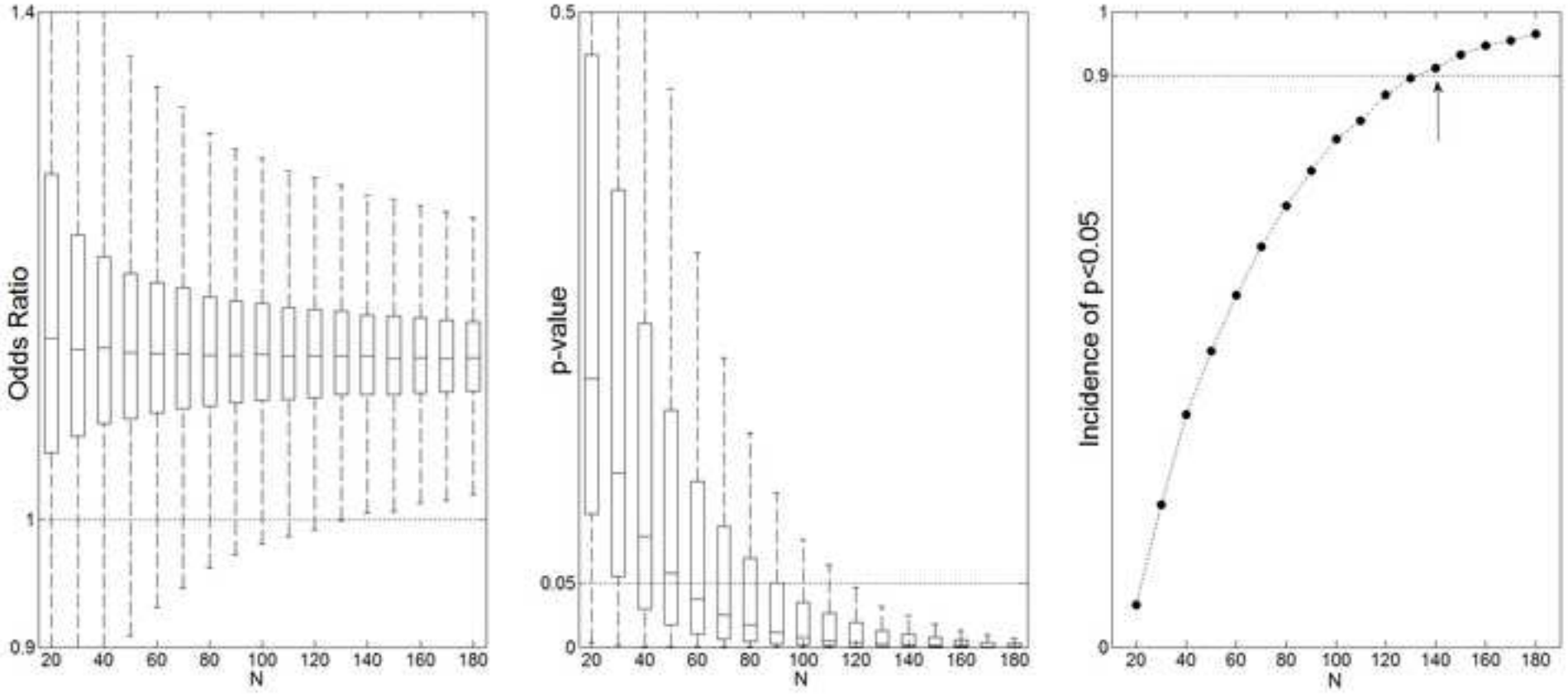

Figure

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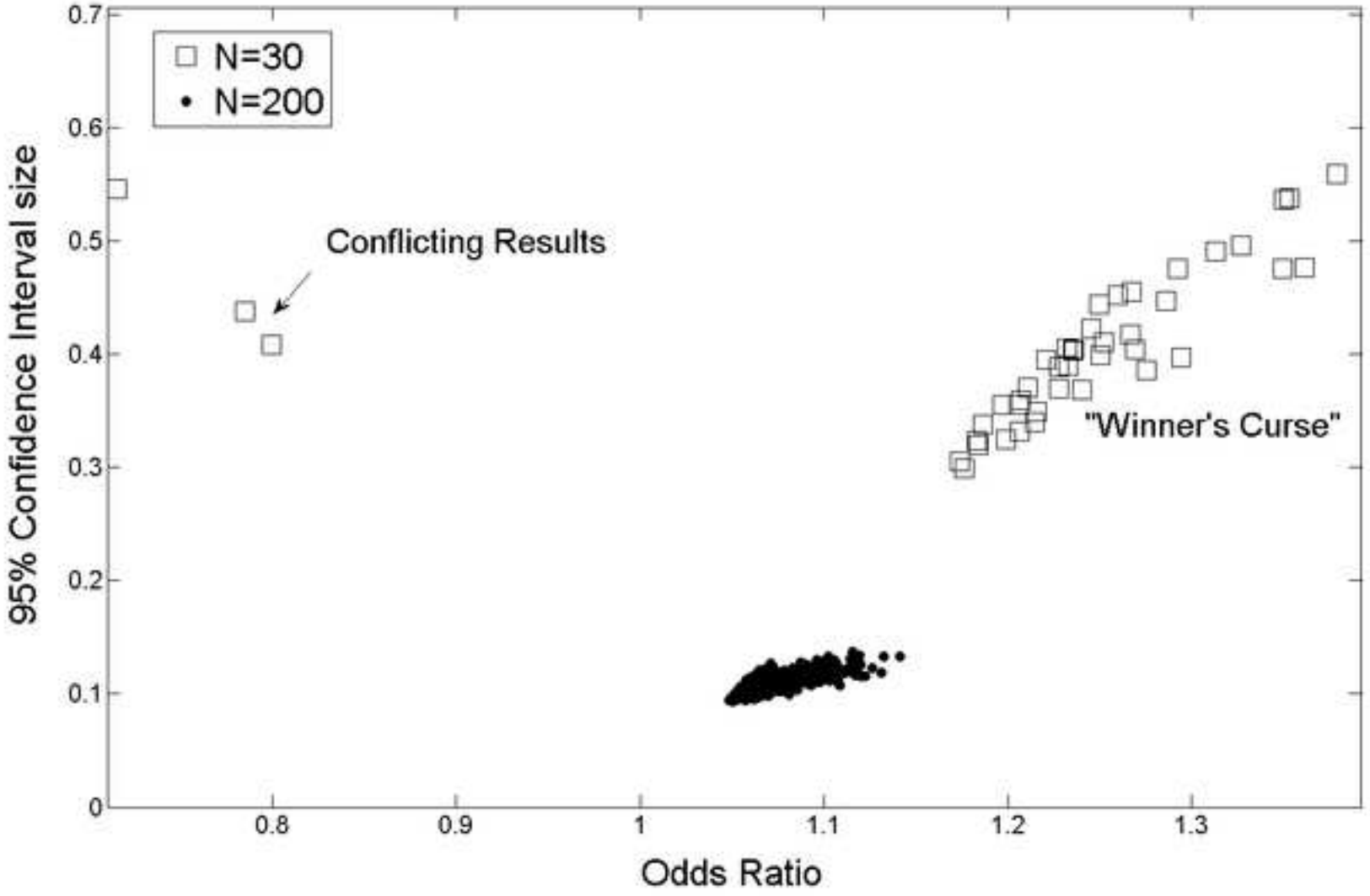

Table

Variable	Outcome					Total
	D	PVS	SD	MD	GR	
ABP	171 (22%)	14 (2%)	241 (31%)	193 (25%)	147 (20%)	766
Age	172 (22%)	15 (2%)	246 (32%)	191 (25%)	149 (19%)	773
AMP	165 (22%)	15 (2%)	244 (32%)	193 (25%)	149 (19%)	766
CPP	171 (22%)	14 (2%)	242 (31%)	193 (25%)	149 (20%)	769
GCS	125 (22%)	8 (1%)	162 (29%)	140 (25%)	122 (23%)	557
ICP	172 (22%)	15 (2%)	244 (31%)	194 (25%)	151 (20%)	776
PRx	156 (22%)	14 (2%)	231 (32%)	180 (25%)	136 (19%)	717
RAP	170 (22%)	15 (2%)	245 (32%)	194 (25%)	149 (19%)	773
Slow	167 (22%)	15 (2%)	244 (32%)	193 (25%)	149 (19%)	768

Table

Dicho	ABP	Age	AMP	CPP	GCS	ICP	PRx	RAP	Slow
1	1300	370	850	550	800	140	140	560	160
2	2300	380	800	450	850	155	150	660	170
3	1200	280	-	-	380	370	190	370	380